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PRODUCT AND KINETIC STUDIES OF THE O-5 AND N⁻-5 BRIDGED CYCLIZATIONS OF A γ-HALOAMIDE*

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Abstract—In the presence of amine bases, the γ-haloamides (II; X = Cl and Br) give, exclusively, the bridged imidate (I) by a reversible first order process (O-5). In most solvents employed, the rate is primarily a function of dielectric constant. In dimethyl sulfoxide, however, rate acceleration is produced by short-range solvent-substrate interaction as well.

In the presence of alkali bases, the γ-haloamides (II) produce, exclusively, the bridged lactam (IV) by an irreversible second-order process (N⁻-5) in which the rate-limiting stage is the displacement of halide ion by amide anion produced, in turn, in a rapid pre-equilibrium step. As expected, the N⁻-5 process is less dependent on solvent polarity than the O-5 process, but, despite obvious differences in their transition state character, rate ratios of bromide to chloride displacement for the two processes are still of the same order (30 for N⁻-5 and 50 for O-5).

Other related displacement reactions of the chloroamide (II) and of the imidate (I) also are described.

THE preparation of the bridged imidate (I) has been reported.[1] Because stable N-substituted 2-iminotetrahydrofurans are rather uncommon,[2,3] and other bridged examples are not known, studies of its chemistry seemed appropriate. It soon became apparent, however, that the cyclizations of the γ-chloro- and -bromoamides (II) readily obtainable from I, provided more interesting objects of study. The transformations to be described first, therefore, mainly provide structural assignments upon which subsequent interpretations of the quantitative cyclization studies are based.

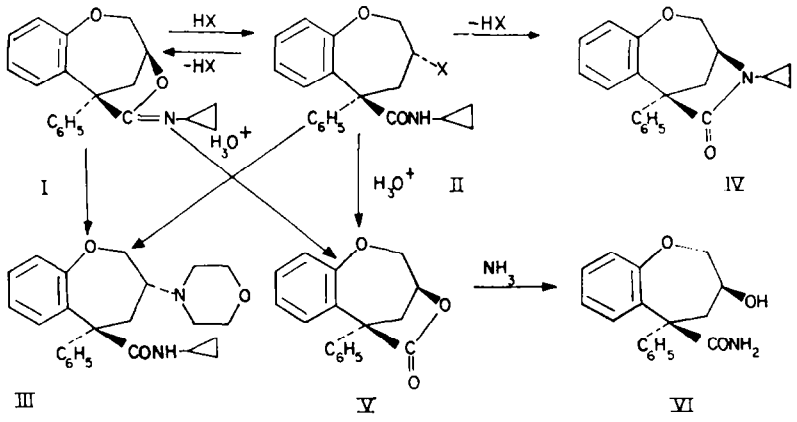
RESULTS AND DISCUSSION

Product studies. Treatment of the imidate (I) with hydrogen chloride or bromide in 2-butanone at room temperature gave the chloro- or bromoamide (II) respectively, in 92 and 61% yields. From the chloroamide (II; X = Cl), the imidate (I) could be regenerated quantitatively by treatment (one week at 40°) with diazabicyclo[2.2.2]-octane (DABCO) in methanol or dimethylformamide (DMF). In molten DABCO (7 hr at 190°) a 78% yield of I was obtained from II (X = Cl).

Although inert to boiling morpholine, the imidate (I) in the presence of added morpholine hydrochloride, gave a 54% yield of the morpholinoamide (III) after 10

* Part XII of the series, *Neighboring Group Reactions*. For part XI, see H. E. Zaugg and R. W. DeNet, *J. Org. Chem.* **29**, 2769 (1964).

[1] H. E. Zaugg and R. J. Michaels, *J. Org. Chem.* **28**, 1801 (1963).
[2] C. J. M. Stirling, *J. Chem. Soc.* 255 (1960).
[3] T. Mukaiyama and K. Sato, *Bull. Chem. Soc. Japan* **36**, 99 (1963).



days at reflux temperature. The identical aminoamide (III) was produced in half this yield (28%) when the chloroamide (II) was boiled in morpholine alone for 11 days. Half of the starting material was recovered.

Acid hydrolysis of the chloroamide (II) gave a 67% yield of the lactone (V) previously obtained[1] (97% yield) in the same manner from the imidate (I). The lactone was further characterized by ammonolysis to the hydroxyamide (VI).

Because the imidate ring in I is necessarily *cis*-bridged, the products (II and III) derived from it by oxygen displacement have been assigned the *trans* configuration. Ample precedent is available to justify the assumption of inversion during nucleophilic reactions involving alkyl-oxygen cleavages of this type.[4] On the other hand, the *cis* configuration is assigned to the hydroxyamide (VI) because alkyl-oxygen fission of the lactone (V) clearly has not occurred.

The fact that III is obtainable from I only in the presence of added morpholine hydrochloride demonstrates a requirement for acid-catalysis. Presumably, a small equilibrium concentration of protonated I represents the electrophilic species in this relatively slow transformation. The much faster formation of II from I despite the involvement of less reactive nucleophiles (halide ion *vs.* morpholine) is then readily accounted for by the virtually complete conversion of I to its reactive protonated form by the halogen acids.

In the conversion of the chloroamide (II) to the aminoamide (III) the intermediacy of I is demonstrated by the fact of overall configurational retention resulting from two successive inversions. The morpholine hydrochloride formed in the first step (II → I) serves to catalyze the second (I → III), further accounting for the fact that III can be formed from II in the absence of exogenous morpholine hydrochloride.

Treatment of II with alkali bases either in hydroxylic or aprotic solvents at 40° gave the bridged lactam (IV) either exclusively or accompanied by smaller amounts of I, depending on conditions. In Table 1 are summarized the results of the reactions of II under a variety of conditions. Product analyses, in most cases, were accomplished by IR assay.

[4a] S. Winstein and R. Boschan, *J. Amer. Chem. Soc.* **72**, 4669 (1950); [b] B. Capon, *Quart. Revs.* **18**, 71 (1964). More precisely, inversion has been repeatedly demonstrated for the reverse process (e.g., II → I) involving neighboring amide group participation. Since facile reversibility of this reaction has been established in the present case, it follows that the process, I → II, also must occur with inversion.

The data of Table 1 show that for the cyclizations leading to I there is a striking dependence on the reaction medium. In solvents of low polarity, whether protic or not (i.e., t-butanol, triethylamine. or 1,2-dimethoxyethane), reaction at 40° is imperceptible. Elevated temperatures effect slow cyclization in 1,2-dimethoxyethane but not in triethylamine. In polar solvents, however, whether protic or aprotic (i.e., methanol or DMF) cyclization occurs smoothly at 40°. These results are in complete

TABLE 1. INTRAMOLECULAR REACTIONS OF THE CHLOROAMIDE II[a]

Base	Solvent	Time, hr	Yield %[b] II	I	IV
None	C_2H_5OH	24–54	70[c]	30[d]	0
None[e]	C_2H_5OH	66	88[c]	12	0
None	DMF[f]	24	95[c]	5	0
DABCO[g]	CH_3OH	23	43	53	0
DABCO	CH_3OH	170	0	100	0
DABCO	DME[g]	170	95	0	0
DABCO	DME	19[h]	35	62	0
DABCO	DMF[f]	23	37	61	0
DABCO	DMF	170	0	99	0
$(C_2H_5)_3N$	$(C_2H_5)_3N$	64[i]	100	0	0
$(C_2H_5)_3N$	$(CH_3)_3COH$	24	100	0	0
NaOH	CH_3OH	23	0	27	73
$NaOCH_3$	CH_3OH	18–24	0	27[k]	72[l]
$NaOC_2H_5$	C_2H_5OH	17–23	0	14[m]	85[n]
$NaOC_2H_5$[o]	C_2H_5OH	20	0	<3	95
NaH	THF[p]	120	0	0	98
NaH	DME	24	0	0	93
NaH	DMF	4	0	7	91
$NaNH_2$	DME	24	53	0	42
$NaNH_2$	DME	170	0	<4	95

[a] According to procedure E, unless otherwise specified. [b] By IR assay. [c] By difference. [d] Average of 3 runs ranging from 29 to 31%. [e] Excess anhydrous HCl was present in the EtOH. [f] 1,4-Diazabicyclo [2.2.2] octane. [g] 1,2-Dimethoxyethane. [h] At 85°, using 7·5 mmoles II and 75 mmoles DABCO in 50 ml solvent. [i] Dimethylformamide. [j] At 78°. [k] Average of 6 runs ranging from 25 to 31%. [l] Average of 6 runs ranging from 70 to 74%. [m] Average of 3 runs ranging from 13 to 15%. [n] Average of 3 runs ranging from 83 to 86%. [o] According to procedure E except that solid II was added in one portion to the solution of the base. [p] Tetrahydrofuran.

accord with the observation that, in these polar solvents in the absence of base, the chloroamide (II) exists in equilibrium with measurable amounts of the imidate salt (I·HCl).[5]

In contrast to this solvent-induced process, cyclization to the lactam (IV) is relatively medium-independent. Reaction takes place in tetrahydrofuran as well as in methanol or DMF. Furthermore, the rate of lactam formation under the conditions

[5] The first entry in Table 1 shows that in EtOH at 40° a steady-state ratio of (I·HCl):II (X = Cl) = 30:70 is attained in 24 hr. The second entry shows that, as expected, addition of HCl displaces the equilibrium in favor of II (X = Cl). The higher equilibrium concentration of II in DMF (Table 1, third entry) as compared to EtOH is very likely a reflection of the greater nucleophilic activity of chloride ion in DMF than in EtOH.[6]

[6] A. J. Parker, *Quart. Revs.* **16**, 176 (1962).

employed in the polar media is faster than imidate formation. Under proper conditions (i.e., addition of the chloroamide to the solution of base) lactam formation occurs to the virtual exclusion of imidate. These findings are consistent with those of Heine[7] in the analogous N-aryl-4-bromobutanamide series and with those observed in other less closely related systems.[8-10]

Rate studies. To investigate the mechanisms of the cyclizations of the haloamides (II) to imidate (I) and lactam (IV) reaction rates were measured at 40° in the presence of varying concentrations of different bases. Results are summarized in Tables 2 and 3. It will be noted (Table 2) that ring-closure leading to I is a first-order reaction (zeroth order in base, hence designated by the symbol O-5[8]) and cyclization leading to IV (Table 3) is second order (first order in base, hence N^{-}-5[8]).

A. *The* O-5 *cyclization.* The observation that conversion of the haloamides (II) to imidate (I) is zeroth order in base, shows that the amine serves merely to displace the rate-limiting equilibrium, II $\rightleftharpoons$ I·HX, in favor of I by "trapping" the HX. Although products were not determined, analogous first order methanolyses of some N-aryl-4-bromobutanamides have been observed previously;[7] and similar first-order O-5 cyclizations have been found and studied extensively in other systems.[8,9]

The qualitative results of Table 1 combined with the quantitative findings summarized in Table 2 show that O-5 cyclization usually depends primarily on the polarity of the environment. O-5 Cyclization, either in nucleophilic triethylamine or in hydrogen-bonding t-butyl alcohol, is just as difficult (qualitatively) as it is in aprotic 1,2-dimethoxyethane. A property common to all three solvents is their low dielectric constant ($\varepsilon < 10$). Furthermore, for the five polar solvents, ethanol ($\varepsilon_{40°} = 22{\cdot}7$[11]), dimethylformamide ($\varepsilon_{40°} = 34{\cdot}2$[12]) ethylene carbonate ($\varepsilon_{40°} = 89{\cdot}4$[13]), N-methylacetamide ($\varepsilon_{40°} = 162{\cdot}4$[12]), and N-methylformamide ($\varepsilon_{40°} = 159{\cdot}2$[12]), encompassing a 7-fold range of dielectric constant, a plot of log $k_{40°}$ *vs.* $1/\varepsilon_{40°}$[14] is linear within experimental error.[15]

Dimethyl sulfoxide, however, with a dielectric constant of only 44·5[16] and a $k_{40°}$ greater than that of N-methylformamide is clearly exceptional. Thus, one more example can be added to the many already known[17] in which dimethyl sulfoxide

[7] H. W. Heine, P. Love and J. L. Bove, *J. Amer. Chem. Soc.* **77**, 5420 (1955).
[8] F. L. Scott, R. E. Glick and S. Winstein, *Experientia* **13**, 183 (1957).
[9] F. L. Scott and D. F. Denton, *Tetrahedron Letters* 1681 (1964).
[10] H. W. Heine, *J. Amer. Chem. Soc.* **78**, 3708 (1956); *Ibid.* **79**, 907 (1957).
[11] *International Critical Tables* Vol. VI, p. 85.
[12] By extrapolation to 40° of values determined at 15°, 20°, 25°, 30° and 35° by G. R. Leader and J. F. Gormley, *J. Amer. Chem. Soc.* **73**, 5731 (1951).
[13] R. P. Seward and E. C. Vieira, *J. Phys. Chem.* **62**, 127 (1958); R. Kempa and W. H. Lee, *J. Chem. Soc.* 1936 (1958).
[14] Compare A. Streitwieser, Jr., *Chem. Revs.* **56**, 603–605 (1956).
[15] A plot on the ordinate of the log $k_{40°}$ values 0·785, 0·973 and 1·161 *vs.* the $1/\varepsilon_{40°}$ values, 0·0440, 0·0292 and 0·0112 for EtOH, dimethylformamide and ethylene carbonate, respectively, gives a slope of $-11{\cdot}4 \pm 0{\cdot}6$. The rate for N-methylacetamide (log $k_{40°} = 1{\cdot}155$) is smaller than would be expected from its polarity ($1/\varepsilon_{40°} = 0{\cdot}0061$) and the rate for N-methylformamide (log $k_{40°} = 1{\cdot}380$; $1/\varepsilon_{40°} = 0{\cdot}0063$) is faster than expected, but addition of these two points to the plot still gives linearity (slope: $-12{\cdot}4 \pm 2{\cdot}8$) within experimental error.
[16] R. K. Wolford, *J. Phys. Chem.* **68**, 3392 (1964).
[17] C. A. Bunton, *Nucleophilic Substitution at a Saturated Carbon Atom* pp. 121–124. Elsevier, New York, N.Y. (1963).

TABLE 2. FIRST ORDER RATE CONSTANTS OF O-5 CYCLIZATIONS OF THE HALOAMIDES II (X = Cl, Br)[a]

Halogen (X =)	Solvent	Base	Base Conc. mole l^{-1}	$10^6 k_1$[b] ± SE sec^{-1}
Cl	C_2H_5OH	DABCO	0·117	6·7 ± 0·6[d]
Cl	C_2H_5OH	DABCO	0·117	6·1 ± 0·3[d]
Cl	C_2H_5OH	DABCO	0·232	5·7 ±0·1[d]
Cl	C_2H_5OH	DABCO	0·210	6·2 ± 0·3[d]
Cl[c]	C_2H_5OH	$(C_2H_5)_3N$	0·144	5·7 ± 0·1
			Mean:	6·1 ± 0·3
Br	C_2H_5OH	DABCO	0·115	310 ± 20[e]
Br	C_2H_5OH	DABCO	0·112	290 ± 40
			Mean:	300 ± 30
Cl	$HCON(CH_3)_2$	DABCO	0·096	10·0 ± 0·3[d]
Cl	$HCON(CH_3)_2$	DABCO	0·112	8·9 ± 0·5[d]
Cl	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·144	9·5 ± 0·3[d]
Cl	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·144	9·1 ± 0·1
			Mean:	9·4 ± 0·3
Br[c]	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·070	50 ± 22[f]
Br[c]	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·144	144 ± 18[g]
Br[c]	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·070	136 ± 10[g]
Br	$HCON(CH_3)_2$	$(C_2H_5)_3N$		295 ± 75[h]
Br[i]	$HCON(CH_3)_2$	$(C_2H_5)_3N$	0·144	375 ± 75[e]
			Mean:	335 ± 75
Cl[i]	$(CH_3O)_2CO$[j]	$(C_2H_5)_3N$	0·144	15·3 ± 0·5[e]
Cl	$(CH_3O)_2CO$[j]	$(C_2H_5)_3N$	0·144	13·7 ± 1·7
			Mean:	14·5 ± 1·1
Cl[i]	$CH_3CONHCH_3$	$(C_2H_5)_3N$	0·144	14·8 ±1·1[e]
Cl[i]	$CH_3CONHCH_3$	$(C_2H_5)_3N$	0·144	13·7 ± 1·2
			Mean:	14·3 ± 1·2
Cl[i]	$HCONHCH_3$	$(C_2H_5)_3N$	0·072	23 ± 2[e]
Cl[i]	$HCONHCH_3$	$(C_2H_5)_3N$	0·144	25 ± 1
			Mean:	24 ± 2
Cl	$(CH_3)_2SO$	$(C_2H_5)_3N$	0·144	38 ± 7[d,e]
Cl[c]	$(CH_3)_2SO$	$(C_2H_5)_3N$	0·144	33 ± 1
Cl[c]	$(CH_3)_2SO$	$(C_2H_5)_3N$	0·144	31 ± 1
Cl[c]	$(CH_3)_2SO$	$(C_2H_5)_3N$	0·144	29 ± 1
			Mean:	33 ± 3

[a] Except where otherwise noted, reaction temp. was 40° ± 1°, and 0·060 M concentrations of haloamide were employed. Reactions were generally carried to 40–80% of completion. [b] Except where otherwise noted, rates were determined by potentiometric titration of halide ion. [c] An 0·030 M concentration of haloamide was used. [d] Determined by IR spectrophotometry. [e] A separate run (at 40°) showed that I is the sole product of this solvolysis. [f] Measured at −23°. [g] Measured at 0°. [h] Determined by linear extrapolation to 40° of the rate constants measured at −23° and 0°. [i] An 0·015 M concentration of haloamide was used. [j] Ethylene carbonate.

TABLE 3. SECOND ORDER RATE CONSTANTS OF N⁻-5 CYCLIZATIONS OF THE HALOAMIDES II (X = Cl, Br) AT 40 ± 0·1°[a]

Halogen[b] II (X =)	Solvent[c]	Base conc. mole/l	$10^3 k_2 \pm$ SE 1 mole^{-1} sec^{-1}
Cl	A	0·113	1·76 ± 0·02
Cl	A	0·113	1·58 ± 0·01
			Mean: 1·67 ± 0·02
Br[d]	A	0·036	53 ± 5
Br[e]	A	0·025	52 ± 1
Br[e]	A	0·025	50 ± 5
			Mean: 52 ± 4
Cl	B	0·060	1·37 ± 0·02
Cl	B	0·068	1·31 ± 0·03
Cl	B	0·068	1·38 ± 0·06
Cl	B	0·113	1·29 ± 0·04
			Mean: 1·34 ± 0·04

[a] Reactions were conducted in the presence of EtONa and, except where noted, with 0·060 M concentrations of haloamide. [b] All reactions were carried to 80–95% of completion. [c] A: 10% v/v 2-butanone in EtOH; B: absolute EtOH. [d] 0·0265 M bromoamide. [e] 0·020 M bromoamide.

accelerates substitution rates by short-range interactions with the substrate, in addition to any ordinary effects due to its bulk polarity.

B. The N⁻-5 *cyclization.* The demonstration of second order kinetics, the observation that the lactam (IV) is formed from the bromoamide (II) thirty times faster than from the chloroamide (II) and the confirmation (Experimental) of rapid NH–ND exchange in the chloroamide (II) all combine to show that the rate-limiting step in the N⁻-5 cyclization is the one involving halide ion displacement by the amide anion. The amide anion is formed in turn in a fast pre-equilibrium step by attack of base on the NH-proton of the neutral amide group. The mechanism is therefore exactly analogous to the one encountered by Zioudrou and Schmir[18] in the formation of oxazolines and dihydro-oxazines from certain amidoalkyl phosphotriesters. In these reactions the intramolecular displacement of phosphodiester groups by amide anion was found to be rate-limiting.

This mechanism also accounts for the observed insensitivity (Table 1) to solvent polarity of the N⁻-cyclization relative to the O-5 cyclization. In the transition state for the N⁻-5 process, the anionic charge is dispersed, but in the O-5 process, charge in the transition state is increased relative to the initial state.[19] Taken in conjunction with Kornblum's generalization[20] about the alkylation of nucleophiles possessing two reactive sites, these considerations lead to a further understanding of the ambident nature of the amide group in II. Relative to the N⁻-5 process, O-5 cyclization requires

[18] C. Zioudrou and G. L. Schmir, *J. Amer. Chem. Soc.* **85**, 3258 (1963).
[19] Compare Ref. 17, pp. 11 and 112.
[20] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Amer. Chem. Soc.* **77**, 6269 (1955).

more bond-breaking (S_N1) character in the transition state. Consequently,[20] the more electronegative oxygen atom serves as the reaction site. Conversely, in the N⁻-5 process, bond-formation (S_N2 character) is more important in the transition state, and the less electronegative nitrogen atom serves as the nucleophilic site. It is interesting to note that, despite these differences in transition state character, rate ratios of bromide to chloride displacement still differ very little for the two processes (30 for N⁻-5 *vs.* 50 for O-5).

EXPERIMENTAL[21]

trans-3-*Chloro*-N-*cyclopropyl*-5-*phenyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-5-*carboxamide* (II, X = Cl)

A suspension of 28·4 g (0·08 mole) of I[1] in 100 ml 2-butanone cooled in ice was saturated with anhydrous HCl. To the resulting clear solution dry ether was added to the point of turbidity, and the mixture refrigerated for 36 hr. The crystallized product (25·3 g, 92%), m.p. 174–177°, was collected at the filter and dried. Recrystallization of a sample twice from 2-butanone gave analytically pure II, m.p. 176–177°; $\lambda_{max}^{CHCl_3}$ (μ) 1·49 (NH), 1·63 (cyclopropyl CH_2), 2·93 (NH), 5·99 (>C=O). (Found: C, 69·92; H, 5·80; N, 4·05. $C_{20}H_{20}ClNO_2$ requires: C, 70·25; H, 5·89; N, 4·10.)

When V[1] and IV were treated with HCl in the foregoing manner, they were recovered quantitatively.

When I was treated with excess 5% HClaq, a clear solution formed at room temp, but on standing, solid precipitated slowly. IR analysis showed it to be a mixture of II and V.

PMR spectrum of the chloroamide (II)

A 60 megacycle spectrum was obtained in 10% $CDCl_3$ solution using TMS as an internal standard. The very complex pattern of multiplets observed is summarized in the following Table in which relative integrated areas are given in proton equivalents assuming the presence of 9 aromatic hydrogens.

Multiplet range c/s from TMS	Assignment cf. II	Relative area
15–60	Cyclopropane CH_2's	3·7
128–162	Cyclopropane CH	1·2
162–250	—C—CH_2—C—Cl and NH	3·0
250–302	—O—CH_2—C—Cl	1·7
320–350	—CHCl	1·0
385–475	Aromatic H's	9·0 (assumed)

trans-3-*Bromo*-N-*cyclopropyl*-5-*phenyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-5-*carboxamide* (II, X = Br)

Substitution of anhydrous HBr for HCl in the above procedure gave a 60% yield of II (X = Br), m.p. 165–166° (from 2-butanone–ether); $\lambda_{max}^{CHCl_3}$ (μ) 1·49 (NH), 1·63 (cyclopropyl CH_2), 2·93 (NH), 5·99 (> C=O). (Found: C, 61·91; H, 5·13; N, 3·52. $C_{20}H_{20}BrNO_2$ requires: C, 62·18; H, 5·22; N, 3·63.)

trans-N-*Cyclopropyl*-3-*morpholino*-5-*phenyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-5-*carboxamide hydrochloride* (III)

A mixture of 6·1 g (0·02 mole) of the bridged imidate I, 2·5 g (0·02 mole) morpholine hydrochloride and 40 ml morpholine was refluxed for 10 days. Excess morpholine was removed by distillation under red. press. the residue was taken up in dry ether and insoluble morpholine hydrochloride (3·1 g) removed by filtration. The filtrate was treated with excess ethereal HCl to precipitate all basic

[21] M.ps are uncorrected.

material. The crude hygroscopic salt mixture was then taken up in water and insoluble material was removed by extraction with $CHCl_3$. The aqueous layer was treated with excess 50% NaOHaq, the precipitated base was then taken up in ether, dried, and reconverted to the salt by the addition of dry ethereal HCl. Collection at the filter followed by two recrystallizations from dry EtOH, and drying *in vacuo* for 3 days at 100°, gave 4·7 g (54%) of III, m.p. 168–169°; $\lambda_{max}^{CHCl_3}$ (μ) 2·97 (NH), 4·4–4·5 (broad, ammonium salt), 6·02 (amide I), 6·76 (amide II). (Found: C, 67·13; H, 6·88; N, 6·55. $C_{24}H_{39}ClN_2O_3$ requires: C, 67·19; H, 6·81; N, 6·53.)

When this reaction was conducted for only 24 hr, 70% of I was recovered. When I was refluxed in morpholine for 24 hr in the absence of morpholine hydrochloride, it was recovered quantitatively.

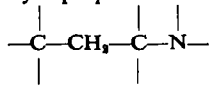
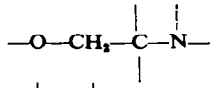
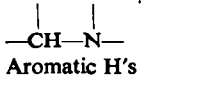
Reaction of the chloroamide (II)

A. *With morpholine.* A solution of 3·0 g (0·009 mole) of II in 20 ml morpholine was refluxed for 11 days. The mixture was worked up essentially as described in the foregoing procedure. From the neutral fraction was obtained 1·5 g (50%, m.p. 174–176°) starting material and from the basic fraction, 1·1 g (28%) of III m.p. 168–169°, identical (mixture m.p., IR spectrum, elemental analysis) with the product obtained from the bridged imidate I.

B. *With DABCO.* A mixture of 2·0 g (0·0059 mole) of II and 11·2 g (0·1 mole) 1,4-diazabicyclo [2.2.2] octane (DABCO) was heated at 190° for 7 hr. The cooled reaction mixture was treated with water (75 ml) and insoluble product (1·8 g, m.p. 182–188°, halogen-free) was collected at the filter and washed with more water. Two recrystallizations from dry EtOH gave 1·4 g (78%) pure bridged imidate I,[1] m.p. 189–190°, identified by mixture m.p. and IR spectrum. (When II was refluxed for 64 hr with excess triethylamine, it was quantitatively recovered.)

C. *With sodium hydride in 1,2-dimethoxyethane—preparation of 4,5-benzo-8-cyclopropylaza-7-keto-3-oxa-6-phenylbicyclo*[4.2.1]*nonane* (IV). To a suspension of 0·32 g (0·0066 mole) 50% mineral oil dispersion of NaH in 1,2-dimethoxyethane (10 ml) was added dropwise with stirring a solution of 2·1 g (0·006 mole) II in the same solvent (30 ml). The mixture was then stirred and warmed at 40° for 48 hr. The mixture was then concentrated to dryness under red. press. The solid residue was washed by trituration and decantation with pentane, dried, resuspended in water (50 ml) and collected at the filter. Drying gave 1·6 g (89%, m.p. 187–190°) of IV. Two recrystallizations from MeOH gave pure IV, m.p. 192–193°; $\lambda_{max}^{CHCl_3}$ (μ) 1·63 (cyclopropyl CH_2), 5·91 (> C=O), no NH or OH absorption; when mixed with a sample of the bridged imidate I (m.p. 190–191°), the m.p. was depressed to 155–165°. (Found: C, 78·90; H, 6·21; N, 4·59. $C_{20}H_{19}NO_2$ requires: C, 78·66; H, 6·28; N, 4·59%.)

PMR spectrum of the lactam (IV). The complex 60 megacycle spectrum in $CDCl_3$ solution is summarized in the following Table.

Multiplet range c/s from TMS	Assignment cf. IV	Relative area
10–66	Cyclopropane CH_2's	3·9
132–182	Cyclopropane CH and 	3·1
215–255		2·1
255–287		1·0
374–482	Aromatic H's	9·0 (assumed)

D. *Hydrolysis to the lactone* (V). A mixture of 2·7 g (0·008 mole) of II, 25 ml 10% HClaq and 10 ml glacial acetic acid was heated on the steam bath for 16 hr. Crystallized product (2·1 g, 100%, m.p. 167–170°) was filtered from the reaction mixture, dried and recrystallized from MeOH to give pure V (1·4 g, 67%), m.p. 171–172°, identified by its IR spectrum and mixture m.p. with an authentic sample.[1]

E. *Quantitative product determinations of the intramolecular reactions of the chloramide* II (Table I). Most of the reactions of Table I were carried out by dissolving 2·56 g (7·5 mmoles) of II in 60 ml solvent, thermostatting at 40 ± 0·2°, and adding excess base (15 mmoles of DABCO, or 8·3 mmoles NaOH, RONa, NaH or $NaNH_2$). After stirring for the length of time indicated, the mixture was poured into ice-water and precipitated product was collected at the filter, dried and weighed. The finely-ground product was submitted to IR assay.

The spectra were determined in $CHCl_3$ solution using a Perkin–Elmer model 21 spectrophotometer. Bands at 2·93, 7·15 and 7·49 microns were used for the analysis of II, IV and I, respectively. Mutual interference at these wavelengths was negligible, and the relationship between concentration and baseline absorbance was found to be linear over the concentration range 0–100% for the 3 pure substances. Lactam and imidate assays were run as 7% solutions in a 0·10 mm cell, and chloroamide determinations as 5% solutions in a 1·0 mm cell (for the 0–10% range) or a 0·5 mm cell (for the 10–100% concentration range). Determinations of the 3 components in a number of ternary synthetic mixtures all gave results within 2% of the known proportions.

F. *Kinetic determinations.* (1) *By IR assay.* A weighed quantity (2·051 g, 6 mmoles) of II in a 100-ml volumetric flask was dissolved in thermostatted abs. EtOH. A known volume of a standardized solution of base [DABCO, $(Et)_3N$ or NaOEt] in preheated dry EtOH was added and the solution was made up to volume with more preheated EtOH. At intervals, 10-ml aliquots were withdrawn from the thermostatted reaction mixture and added to a 60 ml separatory funnel containing 10 ml $CHCl_3$ and 20 ml water. After partitioning, the $CHCl_3$- layer was drawn off, the aqueous layer extracted with another 10-ml portion $CHCl_3$, and the combined $CHCl_3$ extracts were washed with 10 ml water. The $CHCl_3$ solution was concentrated to dryness under red. press. in a tared 50-ml round bottom flask using a rotating evaporator. After drying the residue *in vacuo* at 50° for several hr, it was weighed, and submitted to IR assay for its content of II (procedure E). Product that crystallized from the mixture during the reaction was found to be uncontaminated by II.

The first-order rate constants (k_1) (amine reactions) were calculated using the expression $k_1 t = 2{\cdot}303 \log [II]_0/[II]_t$ where t is time in seconds, $[II]_0$ is the initial concentration of II and $[II]_t$ is its concentration at time t. Plots of t *vs* $\log 1/[II]_t$ gave straight lines, whose slopes and standard errors (SE) were calculated by the method of least squares. Multiplying them by 2·303 gave the rate constants and their standard errors directly.

The second-order rate constants (k_2) (NaOEt reactions) were obtained from the equation $k_2 t = (2{\cdot}303/[B] - [II]_0) \log \{[II]_0([B] - [II]_0 + [II]_t)/[B][II]_t\}$ where [B] is the initial concentration of NaOEt and the other terms are as defined above. Plots of t *vs.* $\log ([B] - [II]_0 + [II]_t)/[II]_t)$ gave straight lines whose slopes and standard errors were determined as indicated above. These were multiplied by $2{\cdot}303/([B] - [II]_0)$ to obtain the values listed in Table 3.

An experimental source of error in the second-order rate determinations in abs. EtOH derives from the time (ca. 15 min) required to effect solution of the chloroamide before the base could be added. However, the solvolysis rate is slow enough so that the error introduced in this way is small compared to the reproducibility (ca. ±10%) of the measurements. In the N⁻-5 cyclizations of the bromoamide, however, an even lower solubilization rate precluded the use of abs. EtOH as solvent. For this reason, the amide was first dissolved in a volume of 2-butanone corresponding to one-tenth of the final volume of the reaction mixture. After thermostatting, this solution was made up to volume with abs. EtOH and EtONa solution. Also, to slow the reaction to a measurable rate, both the substrate and the base concentrations were reduced (Table 3). Fractions taken near the end of the reaction were checked for product composition and found to be composed of IV and not I. For comparison purposes, two N⁻-5 reactions on the chloroamide were conducted in the 2-butanone–EtOH mixture (Table 3, solvent system A) and were found to be slightly, but significantly, faster than those carried out in pure EtOH (B). This is probably a reflection of a slightly higher equilibrium concentration of the amide anion in solvent A than in solvent B. (2) By *potentiometric titration of halide ion.* Five-ml aliquots were withdrawn from the reaction mixture at suitable time intervals and were discharged immediately into 100-ml beakers containing 25 ml distilled water and a few drops of conc. HNO_3. Halide ion concentrations [X^-] were then determined using a Fisher microburet and titrimeter with a standard $AgNO_3$ solution sufficiently concentrated (0·03–0·05N) to give a sharp end-point. Rate constants were calculated as before substituting the expression $[II]_0 - [X^-]$ for $[II]_t$.

G. *Deuterium exchange.* To 0·0433 g (0·0008 mole) MeONa in a 25-ml volumetric flask was added 3 ml of D_2O followed by a solution of 0·5133 g (0·0015 mole) II in 15 ml dry DME. The latter

was rinsed into the volumetric flask with enough DME to bring the solution to volume. After standing at room temp. overnight, the reaction mixture was concentrated to dryness under red. press. using a rotating evaporator. IR examination of the thoroughly dried solid residue showed absence of any NH absorption, but a new peak appeared at 3·94 μ characteristic of ND absorption. Similar results were obtained when the chloroamide was isolated from another reaction with excess MeONa that was less than 5% converted to IV as determined by chloride ion titration. Under these conditions, hydrogen deuterium exchange is clearly much faster than N^{-}-5 cyclization. Indeed, when triethylamine was substituted for the MeONa in the foregoing procedure, complete deuterium exchange was still observed.

cis-3-*Hydroxy*-5-*phenyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-5-*carboxamide* (VI)

A solution of 10 g (0·038 mole) of V in 95% EtOH (25 ml) was heated in an autoclave with excess liquid ammonia (40 ml) at 125° for 8 hr. After distillation of the mixture to dryness, the solid residue was fractionally crystallized from EtOH and an EtOH–2-butanone mixture. There was obtained 3·5 g (35%) of unreacted V and 2·3 g (21%) of VI, m.p. 188–189°; λ_{max}^{Nujol} (μ) 2·95 (w), 3·04 (w), 5·95 (s, amide I), 6·08 (s, amide II). (Found: C, 72·20; H, 6·24; N, 4·88. $C_{17}H_{17}NO_3$ requires: C, 72·06; H, 6·05; N, 4·95%.)

Heating V with piperidine and cyclohexylamine at 100° for 16 hr led, respectively, to 91% and 93% recovery of starting material. However, refluxing V in a mixture of morpholine and morpholine hydrochloride for 10 days gave only a 46% recovery of V. Unfortunately, no pure hydroxyamide could be isolated, although its presence was indicated by the infrared spectrum.

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